

Saluki Tumor Registry update: June 2008

by MaryDee Sist, DVM

The pathologic study of 100 Saluki hearts revealed an alarming incidence of cancer, specifically hemangiosarcoma of the right atrial appendage of the heart. Overall, greater than 50% of the Salukis had some form of cancer. In the health survey conducted by Saluki Health Research, Inc. (SHR) in 2001 and the current SHR/SCOA survey, cancer was ranked second in importance of health concerns by Saluki owners.

To assess the types of cancer that are prevalent in our Salukis, SHR started a neoplasia, or tumor registry. The goal is to identify and classify neoplasms that occur in Salukis and bank the DNA for future examination. This will, hopefully, help explore the frequent types of cancer found in Salukis and provide clues to potential causes and, ultimately, the early diagnosis, treatment and prevention.

In the last six years, I have received 89 tumor samples. These have been examined microscopically by the chief surgical pathologist at the Diagnostic Center for Population and Animal Health, College of Veterinary Medicine, Michigan State University. The growths in the registry represent tumors from all categories (epithelial, mesenchymal, round cell) and are commonly seen in older dogs. Older dogs of all breeds are more likely to have tumor development, both benign (not cancerous) and malignant.

Over 1/3 of the samples submitted were not cancerous.

Of the submitted tumors, 33 were benign and were either from the skin, mammary gland or spleen. Even though any time the spleen is involved, hemangiosarcoma is a possibility. The submitted samples from four fortunate Salukis were a reactive or hyperplastic process and removal of the spleen was curative.

Growths, or neoplasms, can be categorized depending on the origin of the cell type and can be distinguished as benign or malignant according to their morphological characteristics. Malignant neoplasms have different, more aggressive, behaviors and metastatic (spreading) potential. Some benign versus malignant examples of the same cell types are:

- Epithelial: adenoma vs. adenocarcinoma
- Mesenchymal: fibroma vs. fibrosarcoma
hemangioma vs. hemangiosarcoma
lipoma vs. liposarcoma
neurofibroma vs. neurofibrosarcoma
- Round (discrete) cell: plasmacytoma vs. multiple myeloma
lymphoid hyperplasia vs. lymphosarcoma
histiocytoma vs. malignant histiocytosis

Only by having a mass biopsied, and submitting the sample for a microscopic examination by a qualified pathologist, can you get an idea of the prognosis or how

the growth will affect the life of your Saluki.

Twenty-three growths involved the epithelium (or skin). This was not an unexpected finding since these neoplasms are the most readily seen. Fifteen of the epithelial growths were benign while eight were malignant and carried a poorer prognosis. Hemangiosarcoma, a mesenchymal neoplasm, was diagnosed in two of the skin samples, which has been traditionally recognized as a primary site.

Eleven samples were from the mammary gland, with mammary adenocarcinoma being diagnosed the most frequently. This is not unexpected since the majority of the Salukis sampled were unaltered. Early age neutering has been shown to be protective in the development of mammary cancers since most are hormonally dependent. Three samples were cystadenomas and not cancerous, while eight were malignant and had the potential to spread to adjacent glands, lymph nodes, or the lungs.

Fifteen samples from spleens were submitted and four of these were found to be nodular hyperplasia, which is a benign change that occurs commonly in older dogs. Hemangiosarcoma was the primary cancer in five cases. Five other samples were classified as malignant spindle cell (or undifferentiated) sarcomas and one was a lymphosarcoma. There were also undifferentiated sarcomas in three liver samples and one each in bone (tibia), subcutaneous tissue of the paw and of the lumbar area, and lining of the spine. Further evaluation of these samples by immunohistochemical analysis might show whether these are of the same cell line origin as hemangiosarcomas. Various carcinomas were found at a low incidence in the mouth, thyroid gland, lung, bone, intestines and the central nervous system; all carried a poor prognosis.

Hemangiosarcoma was diagnosed in the right atrial appendage in seven of the submitted heart samples. Metastatic hemangiosarcoma was a secondary finding in submitted mesentery, liver, spleen, or lung samples showing how often it had spread to other organs at the time of initial diagnosis. The size of the mass did not necessarily influence the prognosis, since most dogs died from blood loss due to rupture of the hemangiosarcoma.

This registry showed that hemangiosarcoma (HSA) continues to be prevalent in our Salukis, with histologically confirmed HSA in over a third of the samples submitted. Since the diagnosis can often be made by the location and gross appearance of the tumor, I would suspect that samples from many affected Salukis have not been submitted for inclusion in this study. This is unfortunate since the samples are banked for future DNA analysis. The goal is to include these samples in studies exploring the genome for DNA markers for hemangiosarcoma, as well

as other cancers, to potentially identify at risk individuals.

Progress is being made in narrowing the search for DNA markers for various cancers in certain breeds. To aid in this important research which this registry has documented occurring in Salukis, SHR has contributed funds to the following AKC Canine Health Foundation (CHF) Grants (which have been approved for matching funds from the AKC).

2006/2007

- No. 593 - Mapping Genes Associated with Canine Hemangiosarcoma, Dr. Kerstin Lindblad-Toh

2007/2008

- No. 613 - The Prognostic Significance of Chromosome Aneuploidy in Canine Lymphoma, Dr. Breen

- No. 947 A&B - Heritable and Sporadic Genetic Lesions in Canine Osteosarcoma, Drs. Breen and Modiano

- No. 757 A&B - Hereditary Mutations in Genes Associated with Osteosarcoma in Large Dog Breeds, Dr. Lindblad-Toh

SHR has also pledged support for Dr. Modiano's new research project entitled "Genetic Background and the Angiogenic Phenotype in Cancer," that is being submitted for consideration to the CHF. The scientific and lay summaries are included here. You can read more about his ongoing work at http://www.modiololab.org/cancer/cancer_hemangiosarcoma.shtml.

What is clearly apparent is that we need to continue to support cancer studies, especially those related to hemangiosarcoma, to help ensure the future health and welfare of our ancient breed.

For more information on how to submit samples for inclusion into the tumor registry, the protocol is available on the SHR web site: www.salukihealthresearch.tripod.com or contact Dr. Sist at: salukihealth@aol.com, 517-655-1354

Genetic Background and the Angiogenic Phenotype in Cancer

by Jaime F. Modiano, VMD, PhD

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Science summary

In the initial funding period of this AKC CHF-supported project (2005-2007), we showed that hemangiosarcomas (HSAs) from Golden Retrievers have different gene expression profiles than HSAs from non-Golden Retrievers. Our results led us to formulate two complementary hypotheses on the influence of "breed" on behavior and etiology of HSA. For this continuing research project we advance the hypotheses that HSAs from Golden Retrievers, German Shepherd Dogs and Portuguese Water Dogs harbor significantly different gene expression profiles, and that subtle molecular differences alter how cells derived from tumors of each of these three breeds respond to anti-angiogenic therapies. To test these hypotheses, aim 1 will use microarray technology and contemporary bioinformatics to establish unique expression signatures in HSA samples from each breed; aim 2 will test how small molecule inhibitors that act directly and indirectly on angiogenic pathways affect HSA cells derived from dogs of each of these breeds, and aim 3 will examine how attenuating vascular endothelial growth factor receptors affects pro-inflammatory environments generated by HSA cells. Our results will define unique aspects that mediate breed predisposition to HSA, including shared factors that may provide insights to develop more effective strategies for prevention and treatment.

Lay abstract

Certain dog breeds are prone to develop certain types of cancer; yet, there has been little progress to define genes or other factors that account for this risk. Our recent work on hemangiosarcoma is the first to clearly demonstrate that a dog's genetic background, defined by "breed," can influence the profile of genes that are expressed by tumors. Among other important implications, this suggests that certain breeds are diagnosed with specific cancers more frequently than others because of the behavior of tumors after they arise, and not simply because they arise more frequently. Specifically, this may apply to the observed predisposition for hemangiosarcoma seen in Golden Retrievers, German Shepherd Dogs, and Portuguese Water Dogs. In addition, "one-size-fits-all" therapies may be inadequate to effectively treat this disease. This project will extend our observations on gene expression profiles in hemangiosarcoma from Golden Retrievers to German Shepherd Dogs and Portuguese Water Dogs, and it also will define how new targeted therapies may effectively control the disease in these and other dog breeds.

Dr. Modiano also states that, "While we recognize the importance of doing this in more breeds, limitations of budget and manpower force us to prioritize our approaches. The two breeds we chose represent a substantial population of dogs at risk that is not closely related to Golden Retrievers and that have a dedicated following, allowing for maximum diversity in the analyses and for efficient recruitment. As we build more data, the addition of new breeds should become easier (and somewhat less costly), so we expect that all dogs eventually will benefit from data targeted to just a few breeds. Moreover, while differences we identify may inform how risk has become embedded in distinct breeds, similarities among breeds will be equally or more important to help us develop strategies from prevention and treatment."